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Vitamin D level is inversely related to allergen sensitization for risking atopic dermatitis in early childhood

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ABSTRACT

Background: There are few studies concerning the impact of serum vitamin D status on the risk of allergen sensitization and atopic dermatitis (AD) during early childhood.

Method: Children with AD and age-matched healthy controls (HC) were prospectively enrolled at age 0.5, 2, and 4 years. Serum 25-hydroxyvitamin D (25[OH]D) level was measured using Elecsys Vitamin D Total assay. The study utilized the ImmunoCAP assay to analyze specific IgE for food and inhalant allergens, along with total serum IgE levels. It explored the connection between vitamin D levels and allergen sensitization, as well as their influence on AD at different ages.

Results: A total of 222 children including 95 (59 AD and 36 HC), 66 (37 AD and 29 HC), and 61 (32 AD and 29 HC) children were classified at age 0.5, 2, and 4 years, respectively. In children with AD, there was a significantly lower vitamin D level at age 2 and 4, but a significantly higher prevalence of food and mite sensitization at all ages in comparison with HC ($P < 0.001$). Vitamin D level was found to be inversely related to the prevalence of allergen sensitization at age 4 ($P < 0.05$). However, vitamin D level appeared to have high importance for allergen sensitization at all ages and AD at age 2 and 4 years.

Conclusion: Vitamin D deficiency is strongly associated with heightened prevalence of allergen sensitization, potentially increasing the susceptibility to AD in early childhood.

Keywords: Allergen sensitization, Atopic dermatitis, Vitamin D, 25-hydroxyvitamin D

INTRODUCTION

Vitamin D, an essential immunomodulator in both innate and adaptive immune responses, is known to be implicated in childhood atopic dermatitis (AD).[1,2] Many studies have additionally documented the inverse association between serum vitamin D levels and the risk of developing AD.[3] There are, however, limited research exists regarding the correlation between vitamin D levels and AD across various age intervals during early childhood.

Allergen sensitization generally arises first to food allergens in infancy and to aeroallergens later in childhood.[4] Several studies have shown that serum

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vitamin D status is inversely related to specific allergen sensitizations and total serum IgE levels in early childhood.[5,6] Clinically, sensitization to allergens is consistently viewed as a potential trigger factor for AD.[7,8] However, a comprehensive exploration of the connection between serum vitamin D levels, allergen sensitizations, and AD is still lacking.

This study seeks to establish the serum vitamin D levels in children with AD at ages 0.5, 2, and 4 years. It aims to uncover the association between vitamin D levels and childhood AD across different age groups. Furthermore, the research aims to probe the potential influence of vitamin D on allergen sensitization and AD at distinct stages of childhood.

MATERIALS AND METHODS

Study population and data collection

This prospective case control study was performed to examine the association between serum vitamin D levels, allergen sensitization, and AD in infancy and early childhood. The diagnosis of AD was assessed by the physicians in outpatient clinics based on the Hanifin and Rajka criteria.[9] Healthy controls (HC) were defined as children without AD or a history of allergic reactions or infections. Subjects with confirmed AD and age-matched HC were enrolled at 0.5, 2, and 4 years of age separately. Comprehensive data encompassing demographic data, vitamin D supplement, gestational age, maternal age at delivery, family atopy history, parental smoking, seasons of birth, and breastfeeding pattern during infancy was collected. This study was approved by the Institutional Ethics Committee of Chang Gung Memorial Hospital (No. 201900377A3). Written informed consent was acquired from the parents or guardians of all enrolled participants in the study.

Measurement of 25(OH)D levels

Serum samples were collected and frozen at −80 °C until examined. The serum levels of 25(OH)D were measured using the Elecsys Vitamin D Total assay (Roche Diagnostics, Mannheim, Germany), a newly automated electrochemiluminescence-based method. This assay featured measurement of the total 25(OH)D level as both 25(OH)D2 and 25(OH)D3 with good precision (coefficient of variation <13.6%) and excellent correlation with liquid chromatography-mass spectrometry.[10] Serum 25(OH)D levels of <20 ng/ml, 20–29.9 ng/ml, and ≥30 ng/ml were defined as deficiency, insufficiency, and sufficient status respectively, as described in literature.[11]

Total serum immunoglobulin E and allergen-specific immunoglobulin E levels

Serum samples of children at different years of age were collected and measured. Simultaneous measurements were conducted for total IgE levels and specific IgE targeting the two most prevalent food allergens (egg white, milk), as well as inhalant allergens (*D. pteronyssinus* and *D. farinae*). Total serum IgE level was determined using ImmunoCAP (Phadia, Uppsala, Sweden), with IgE levels ≥100 kU/L indicating IgE sensitization.[12] Allergen-specific IgE was examined by ImmunoCAP Phadiatop Infant, a commercially available IgE assay, with allergen sensitization defined as values ≥ 0.35 kU/L.[13]

Statistical analysis

Baseline characteristics, categorized by different vitamin D status, were compared using suitable univariable parametric and non-parametric tests, including ANOVA, Kruskal-Wallis test, and Chi-squared test as applicable. Statistical analysis between two groups was performed using Chi-squared test and Mann-Whitney test. Random Forest models were constructed to rank the importance of potential factors regarding allergen sensitization and AD. The Boruta feature selection algorithm was employed for validation, with a 20-fold stratified cross-validation conducted using R software (version 3.5.3, Lucent Technologies, NJ, USA).[14] Statistical analysis was carried out using the Statistical Program for the Social Sciences (IBM SPSS Statistics for MAC, Version 25.0, Armonk, NY, USA). Graphs were generated using GRAPHPAD PRISM Version 8.0 software (GraphPad Software Inc, La Jolla, CA, USA). All hypothesis tests were two-tailed, and significance was established at a *P*-value below 0.05.

RESULTS

Population characteristics

A total of 222 children were prospectively enrolled in this study, including 95 (59 AD and 36

HC), 66 (37 AD and 29 HC), and 61 (32 AD and 29 HC) children at age 0.5, 2, and 4, respectively. Children were subdivided further into 3 groups based on serum 25(OH)D status. Table 1 illustrates the baseline characteristics according to serum 25(OH)D status within various age groups. Children with serum 25(OH)D levels <20 ng/ml exhibited significantly higher prevalence of exclusive breastfeeding (BF) and maternal atopy, in contrast to those with serum 25(OH)D levels ≥30 ng/ml, at both 0.5 years of age ($P < 0.001$) and 4 years of age ($P = 0.010$). No statistically significant disparity in vitamin D supplementation was observed across varying 25(OH)D statuses at the 3 distinct age points.

Serum 25(OH)D levels and allergen sensitization prevalence between AD and HC

Fig. 1 shows the comparisons of serum 25(OH)D levels and the prevalence of food and mite sensitizations between AD and HC at varying ages. In comparison to HC, children with AD exhibited notably reduced serum 25(OH)D levels at ages 2 and 4 ($P < 0.001$), while no such distinction was observed at age 0.5 (Fig. 1A). However, children with AD were found to have significantly higher vitamin D supplement usage in comparison with HC at age 0.5 ($P = 0.004$). Significantly higher prevalence of food sensitization was observed in children with AD at both age 0.5 ($P < 0.001$) and age 4 ($P < 0.01$). However, children with AD demonstrated notably increased prevalence of mite and IgE sensitization at ages 2 and 4 ($P < 0.001$), but not at age 0.5 (Fig. 1B).

Association between serum 25(OH)D status and allergen sensitization prevalence

Comparisons of the prevalence of food, mite, and IgE sensitization among distinct serum 25(OH)D statuses at 0.5, 2, and 4 years of age are shown in Fig. 1C. In comparison to children with serum 25(OH)D levels ≥30 ng/ml, those with serum 25(OH)D levels <20 ng/ml exhibited a relatively greater prevalence of food sensitization at age 0.5 and mite sensitization at age 2. However, a statistically significant elevation in the prevalence of mite and IgE sensitization was detected solely in children with serum 25(OH)D levels <20 ng/ml at age 4 ($P < 0.05$).

Risk factors for AD and allergen sensitization

Random forest models based on potential factors for AD at different years of age are shown in Fig. 2. Food sensitization and maternal atopy were the variables with high importance rank for AD at age 0.5. By contrast, vitamin D levels and mite sensitization were ranked in the highest importance quartile at age 2 and 4 (Fig. 2A). Most importantly, vitamin D levels were found to have high importance for food sensitization only at age 2, but for mite sensitization at age 2 and 4 (Fig. 2B).

DISCUSSION

Vitamin D has been regarded as an essential immune modulator, taking part in the development of childhood AD. Nevertheless, the connection between serum vitamin D levels, allergen sensitization, and their implications for early childhood AD remains inadequately documented. This study has provided evidence of a robust association between vitamin D deficiency and allergen sensitization, a significant factor for developing AD, suggesting that a deficiency of vitamin D may contribute to AD through the alternation of immune reactions to allergens in early childhood.

The relationship between vitamin D and BF has been reported worldwide. Exclusively breastfed infants are notably prone to vitamin D deficiency, as observed in this study.[15] However, a significant association of vitamin D deficiency with exclusive BF only at age 0.5 may be due to the dietary change from milk to solid food in later childhood. There is also increasing evidence supporting links between vitamin D and allergic disease development.[16,17] Clinically, maternal atopy is recognized as an significant risk factor for childhood asthma,[18] which might specifically elucidate the robust link observed between maternal atopy and childhood vitamin D deficiency in this study.

Vitamin D deficiency is well known to be linked with AD.[19] However, no difference between children with AD and HC at age 0.5 observed in this study may be due to the encouragement of vitamin D supplementation during infancy. Furthermore, allergen sensitization plays a crucial role in the

Characteristics	0.5 yr				2 yr				4 yr			
	25(OH)D levels, ng/ml											
	<20 (n = 21)	20-29.9 (n = 11)	≥30 (n = 63)	*P*-value	<20 (n = 4)	20-29.9 (n = 19)	≥30 (n = 43)	*P*-value	<20 (n = 15)	20-29.9 (n = 25)	≥30 (n = 21)	*P*-value
Age, yr	0.5 ± 0.1	0.5 ± 0.2	0.5 ± 0.2	0.222	2.2 ± 0.4	1.8 ± 0.7	2.1 ± 0.4	0.178	5.1 ± 1.2	4.8 ± 0.7	4.4 ± 0.6	0.070
Sex, male	61.9%	45.5%	63.5%	0.525	50.0%	63.2%	51.2%	0.67	46.7%	44.0%	66.7%	0.270
Vitamin D supplement	4.8%	20.0%	13.3%	0.420	0%	11.8%	7.0%	0.688	0.0%	0.0%	9.5%	0.154
Body mass index, kg/m^2	17.1 ± 1.3	17.2 ± 1.7	17.3 ± 1.8	0.852	15.1 ± 2.0	16.7 ± 1.9	16.3 ± 1.6	0.559	15.5 ± 1.3	16.1 ± 2.4	15.2 ± 1.2	0.238
Maternal age, yr	33.1 ± 3.5	33.0 ± 3.4	32.1 ± 4.6	0.406	34.2 ± 3.0	33.5 ± 5.0	32.8 ± 4.8	0.872	34.8 ± 4.4	33.6 ± 5.6	33.6 ± 4.5	0.742
Gestation age, wk	37.7 ± 2.4	38.3 ± 1.8	37.9 ± 1.7	0.891	39.0 ± 1.0	38.6 ± 0.9	38.0 ± 1.8	0.363	38.1 ± 1.6	38.4 ± 1.2	38.3 ± 1.9	0.898
Parental atopy	85.7%	90.0%	71.7%	0.245	100.0%	77.8%	75.0%	0.608	92.9%	72.0%	66.7%	0.194
Maternal atopy	71.4%	50.0%	43.3%	0.086	100.0%	55.6%	52.5%	0.279	57.1%	68.0%	23.8%	**0.010**
Parental smoking	21.1%	30.0%	26.8%	0.842	0.0%	25.0%	45.9%	0.187	38.5%	34.8%	31.6%	0.922
Seasons of birth												
Spring	23.8%	10.0%	40.0%	0.384	33.3%	22.2%	20.0%	0.076	21.4%	32.0%	19.0%	0.916
Summer	42.9%	40.0%	23.3%		66.7%	27.8%	30.0%		28.6%	24.0%	38.1%	
Fall	14.3%	30.0%	18.3%		0.0%	50.0%	22.5%		21.4%	20.0%	14.3%	
Winter	19.0%	20.0%	18.3%		0.0%	0.0%	27.5%		28.6%	24.0%	28.6%	
BF pattern > 6M[a]												
Exclusive BF	76.2%	40.0%	21.7%	**<0.001**	66.7%	55.6%	25.0%	0.166	14.3%	32.0%	42.9%	0.141
Partial BF	23.8%	20.0%	53.3%		33.3%	33.3%	57.5%		78.6%	52.0%	33.3%	
Formula	0.0%	40.0%	25.0%		0.0%	11.1%	17.5%		7.1%	16.0%	23.8%	

Table 1. Baseline characteristics of 222 children in relation to serum 25(OH)D status in different years of age groups. *Data shown are mean ± SD or number (%) of patients as appropriate. AD, atopic dermatitis; BF, breastfeeding; M, month; wk, week; yr, year.All P-values <0.05, which is in bold, are significant. [a]BF pattern > 6M means breastfeeding persists for at least 6 months after birth*

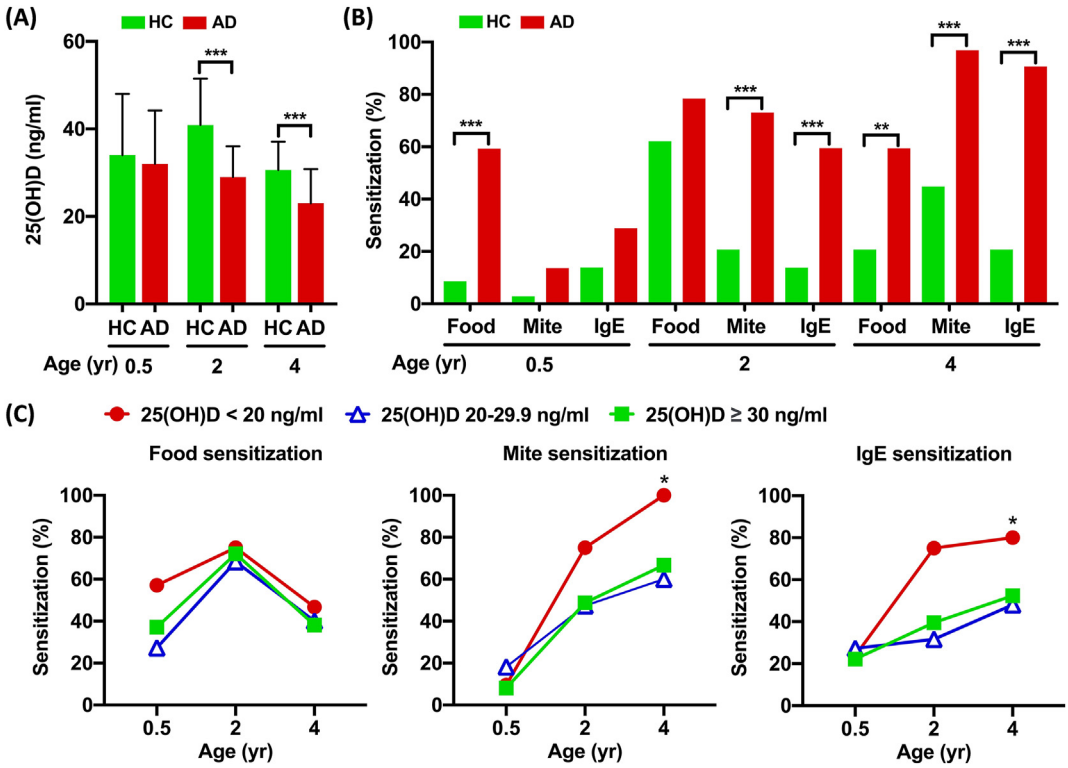

Fig. 1 Associations of serum 25(OH)D status with AD and allergen sensitization at different years of age. Comparisons and differences of the serum 25(OH)D levels (A) and the prevalence of food, mite, and IgE sensitization (B) between AD and HC and between serum 25(OH)D status (C) at age 0.5, 2, and 4 years. Data shown are mean ± SD or percent (%) of patients as appropriate. *P*-values referred to the comparisons of mite [serum 25 (OH)D < 20 ng/ml vs. serum 25(OH)D 20–29.9 ng/ml vs. serum 25(OH)D ≥ 30 ng/ml] and IgE [serum 25 (OH)D < 20 ng/ml vs. serum 25(OH)D 20–29.9 ng/ml] sensitization at age 4 are indicated by the marker. *$P < 0.05$; ***$P < 0.001$

development of atopic diseases.[20] It has been reported that food sensitization occurs commonly in infancy in comparison with the rising prevalence of mite sensitization later in early childhood.[17] In children with AD, a significantly elevated prevalence of food and mite sensitization seen in early and late childhood subsequently supports the idea of a strong association between AD and allergen sensitization.[21]

Vitamin D is an important immune system regulator promoting the anti-inflammatory effects of allergy through Th2 cell suppression and IgE production inhibition in B cells.[22] In this study, findings underscore the significance of vitamin D in food sensitization at age 2, supporting earlier evidence suggesting that insufficient vitamin D levels could elevate the risk of food allergies, particularly prominent in the second year of life.[23] Furthermore, this investigation demonstr-ates vitamin D's association with early childhood mite sensitization, aligning with prior research that observed a negative correlation between vitamin D levels and mite-specific IgE levels during this developmental stage.[24] Consequently, this study corroborates previous research by highlighting a notable relationship between vitamin D deficiency and allergen sensitization.[25,26] Furthermore, food sensitization in infancy and mite sensitizations in early childhood were significant factors for contributing to AD in this study. These findings indicate that vitamin D might be involved in the relationship between allergic reactions to allergen and AD.

Numerous studies have highlighted the substantial correlation between allergic responses to allergens and AD, as in this study.[21,27] Most importantly, in this study, it was observed that vitamin D deficiency heightened the risk of allergen sensitization during early childhood. Furthermore, a dynamic change in sensitization to allergens in early life[17] is consistent with the findings relating vitamin D levels and risk for food and mite sensitization in early and later years, respectively, in this study. In addition, vitamin D serves as an important immune modulator, potentially influencing allergic immune responses and

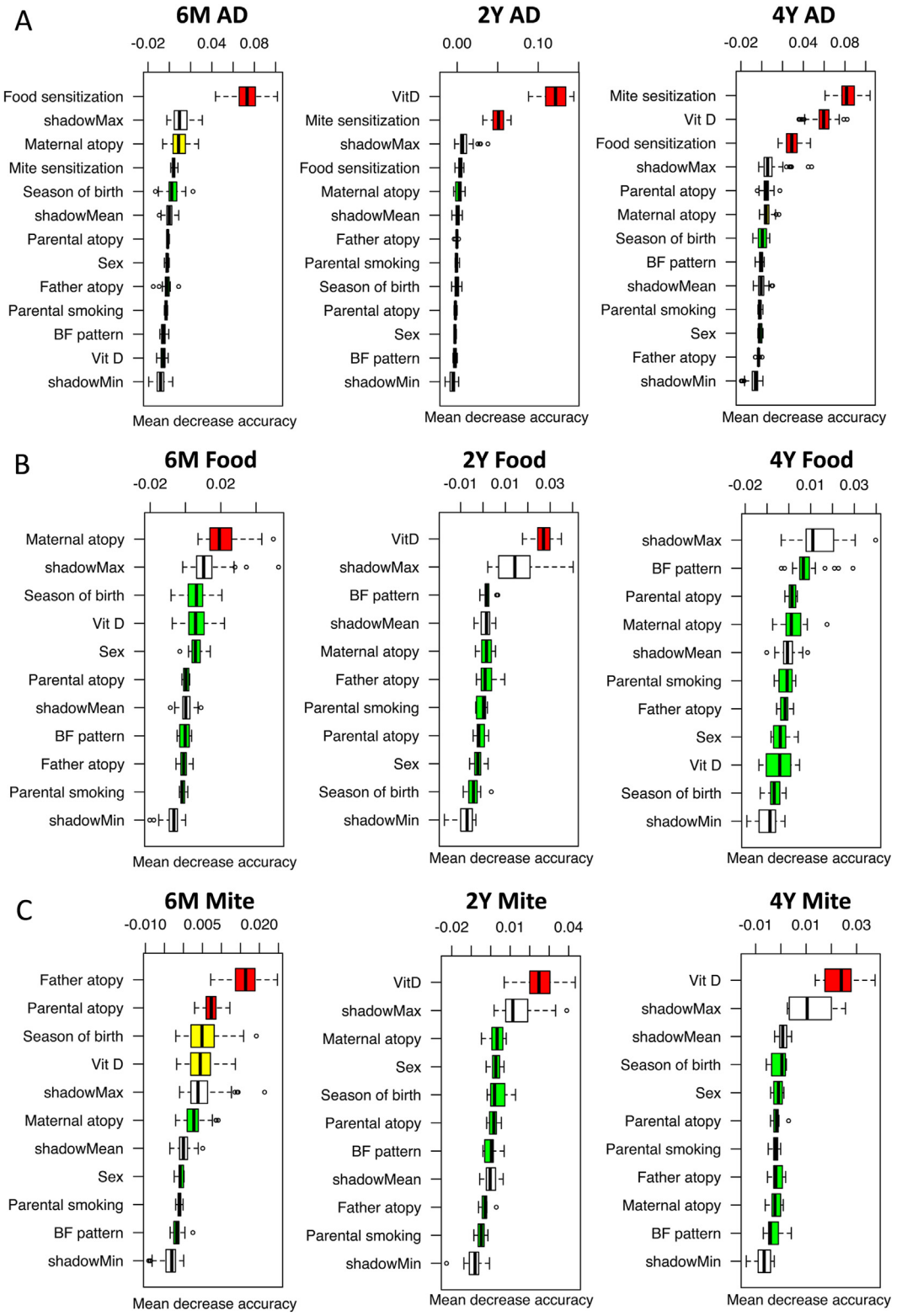

Fig. 2 Random Forest models based on the potential factors for AD (A), food sensitization (B), and mite sensitization (C) at age 0.5, 2, and 4 years. Markers of their importance to the accuracy of the model are ranked in descending order. The boxes indicate 25th–75th percentiles, and black lines represent the mean

susceptibility to allergies.[28] These results indicate that vitamin D deficiency may notably alter the immune reactions to allergens contributing to childhood AD.

A primary limitation of this study is the relatively small sample size, which may limit the ability to detect statistical differences within subgroups. A lack of longitudinal analysis of same subjects has also limited the understanding of the sequential change in serum vitamin D and allergen specific IgE levels. Consequently, the significant relationship observed within this study cannot warrant recognition as a causal association. Moreover, this study did not specifically delve into the exploration of potential antigen exposure on compromised skin in children with AD, which could potentially contribute to allergen sensitization.[29] However, the strength of this study lies in its age-based and age-matched grouping of the subjects at different ages, potentially providing the generalizability of the statistical findings to the populations, and sampling variability during early childhood making our results valid and generalizable.

In conclusion, a vitamin D deficiency appears to be related to exclusive BF and allergen sensitization contributing to childhood allergies. Vitamin D deficiency is strongly associated with AD and a significantly higher prevalence of allergen sensitization during early childhood. Furthermore, vitamin D is an important factor for allergic sensitization risking the development of AD, suggesting that vitamin D deficiency may alter the immune reactions to allergens contributing to AD in early childhood. However, larger longitudinal cohort and molecular studies are required to provide evidence of vitamin D-related biological mechanisms of allergic immune response in AD development.

Abbreviations
AD: atopic dermatitis; HC: healthy controls; BF: breastfeeding.

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Data availability
All the data are included in this paper.

Author contributions
C.-H.S. drafted and revised the manuscript. C.-B.C. performed experimental work and interpretation. M.-H.C. and C.-N.K. performed statistical analyses and presented the data. W.-H.C. and Y.-K.L. were responsible for clinical evaluation of the children and data collection. C.-Y.C. design and supervised the study. All authors discussed the results and approved the final manuscript.

Ethics approval
This study was approved by the Institutional Ethics Committee of Chang Gung Memorial Hospital (No. 201900377A3).

Consent for publication
All authors have agreed with this publication in the World Allergy Organization Journal.

Declaration of competing interest
All the authors declare no conflicts of interest in relation to the present study.

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